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Award Number: W81XWH-13-1-0325

TITLE: Developing Novel Therapeutic Approaches in Small Cell Lung Carcinoma Using Genetically Engineered Mouse Models and Human Circulating Tumor Cells

PRINCIPAL INVESTIGATOR: Jeffrey Engelman MD PhD

CONTRACTING ORGANIZATION: Massachusetts General Hospital

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REPORT DATE: October 2015

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: (Check one)

Approved for public release; distribution unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	**2. REPORT TYPE**	**3. DATES COVERED** *(From - To)*
October 2015	Annual	15 Sep 2014 - 14 Sep 2015

4. TITLE AND SUBTITLE
Developiing Novel Therapeutic Approaches in Small Cell Lung Carcinoma Using Genetically Engineered Mouse Models and Human Circulating Tumor Cells

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-13-1-0325

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Jeffrey Engelman MD PhD

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Massachusetts General Hospital 55 Fruit St
Boston MA 02114

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
US Army Medical Research and Materiel Command
Fort Detrick, MD 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

We have successfully developed mouse models in which to perform in vivo experiments, as well as developed expertise in live animal imaging to enable monitoring to tumors over time in these models. We have initiated treatment studies with chemotherapy and with targeted therapies in our models. Our preliminary data indicate that tumor response to chemotherapy in our models is modest. However, we find that tumor response to combination targeted therapy is significantly superior to either targeted therapy alone or to no treatment. Correlative biomarker studies are underway, including the isolation and enumeration of circulating tumor cells from SCLC patients. These findings support further development of this combination therapy approach and we anticipate ongoing experiments to assess correlative biomarkers.

15. SUBJECT TERMS
Small cell lung cancer (SCLC), Genetically engineered mouse model (GEMM), BH3 mimetic, TORC inhibitor, Apoptosis, Preclinical therapeutics

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	14	**19b. TELEPHONE NUMBER** *(include area code)*

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INTRODUCTION

Small cell lung cancer (SCLC) is an aggressive neuroendocrine carcinoma with a median survival of less than one year and a five-year overall survival of under 2% in the metastatic setting. While chemotherapy initially induces a response in most patients, metastatic disease invariably recurs rapidly and is often resistant to additional conventional therapies. To date, there are no effective targeted therapeutic approaches in SCLC and research efforts to develop new therapeutic strategies for these cancers have lagged far behind those for non-small cell lung cancer. This project aims to address these fundamental challenges by utilizing genetically engineered mouse models (GEMMs) of SCLC that faithfully recapitulate the human disease, as well as circulating tumor cells (CTCs) from both the GEMMs and human SCLC patients to develop a new therapeutic approach. Our therapeutic strategy, the combination of a BH3-mimetic and an mTOR complex (TORC) catalytic site inhibitor, is based on our understanding of the mechanisms of apoptosis and growth arrest in SCLC tumors. Our project aims to (1) explore the mechanism of chemotherapy response and resistance in the GEMM, (2) investigate the activity of combination BH3-mimetic and TORC inhibition therapy in the GEMM, and (3) utilize patient-derived CTCs to monitor treatment response. This report reviews our progress during the second year of funding.

KEYWORDS

Small cell lung cancer (SCLC)
Genetically engineered mouse model (GEMM)
BH3 mimetic
TORC inhibitor
Apoptosis
Preclinical therapeutics

ACCOMPLISHMENTS

Major goals of the project

Specific Aims:

Specific Aim 1: Determine biomarkers of response and resistance to standard chemotherapy in SCLC GEMMs.
Specific Aim 2: Perform preclinical study of combination targeted therapy in SCLC GEMMs.
Specific Aim 3: Utilize patient-derived CTCs as a means to monitor treatment response and predict sensitivity to treatment.

Major Tasks (as detailed in the Statement of Work, modified 9/22/14):

Please see Appendix 1, Statement of Work for MGH.

1. Analyze CTCs from SCLC patients at MGH enrolled on DF/HCC protocol 05-300

Accomplishments under these goals

- **Major Task 8:** The goal of this task is to analyze CTCs from patients with SCLC to assess for changes in CTC number and expression of markers relevant to our combination treatment strategy (P-4EBP1, P-S6, BIM, Bcl-2, Bcl-xL, and Mcl-1

using ISH and IHC) over the course of chemotherapy treatments.

This work will be performed entirely at MGH under the direction of Dr. Engelman. As we described in a prior submission requesting changes to the Statement of Work, Dr. Engelman's group has proposed what we believe to be an improved approach for accomplishing this task. The original grant proposal had described accomplishing this Aim by using the herringbone chip (Maheswaran et al., 2008; Nagrath et al., 2007; Yu et al., 2012). This technology captures cells to a device and allows for enumeration and IHC and in-situ hybridization (ISH) on CTCs, but does not enable collection or propagation of live CTCs. Recently, the Haber and Toner labs at MGH have developed a microfluidic-based live CTC capture platform, the CTC-iChip (Karabacak et al., 2014; Ozkumur et al., 2013). Using antigen-based removal of leukocytes and granulocytes, this technology enables unbiased collection of unperturbed live CTCs in suspension. The Engelman group now proposes to leverage CTC-iChip technology to generate mouse xenograft models directly from SCLC CTCs. Generation of SCLC "CTC-derived xenografts" (CDXs) has recently been described (Hodgkinson et al., 2014). The Engelman group proposes generate xenografts in a similar manner. CTC enrichment from whole blood will be performed using the ^{neg}CTC-iChip and ^{pos}CTC-iChip platforms (Karabacak et al., 2014; Ozkumur et al., 2013). They will quantify the number of enriched CTCs per mL of whole blood using histologic stains and neuroendocrine marker immunofluorescence. Collected CTCs in suspension will then be mixed with an equal volume of matrigel and directly transplanted subcutaneously (SC) into the flanks of NOD/SCID mice that lack the interleukin-2 gamma receptor (NSG mice) (Quintana et al., 2012; Quintana et al., 2008). They will measure tumor dimensions at least three times weekly to determine the efficiency and kinetics of CDX generation. They will utilize these CDX models to perform the molecular analyses outlined in the original proposal. CDX tumors from CTCs isolated before and after chemotherapy treatment will be interrogated for relative expression of TORC1 pathway mediators (P-S6, P-4EBP1) and apoptosis mediators (Bcl-2, Bcl-xL, BIM, Mcl-1) to determine if measurement of these molecular markers will be informative in clinical development of this novel therapy. Notably, the overall enrollment goal has been reduced to 20 patients given the added resources needed for taking the approach detailed above.

PDX	Stage	# Prior Tx	PDX source	P0 latency (days)
MGH1501	LS	0	CTC	76
MGH1504	LS	0	CTC	160
MGH1505-2	ES	4	CTC	108
MGH1506	ES	1	CTC	133
MGH1508	ES	4	CTC	201
MGH1512-A	ES	2	Bx (neck LN)	60
MGH1512-B	ES	2	Bx (neck LN)	64
MGH1514	ES	0	CTC	130
MGH1514-4	ES	3	CTC	31
MGH1515	ES	0	CTC	108
MGH1517	ES	0	Bx (brain)	145
MGH1518-B	ES	0	Bx (paratrach mass)	127
MGH1518-C	ES	0	Bx (paratrach mass)	81
MGH1521-A	ES	0	CTC	74
MGH1522	ES	0	Bx (liver met)	54
MGH1523-B	ES	0	Pleural Effusion	31
MGH1524	ES	0	CTC	83
MGH1525	ES	0	CTC	45

Table 1: MGH SCLC CDX/PDX models. LS: limited stage. ES: extensive stage. Tx: lines of treatments. Bx: Biopsy. LN: Lymph node. P0 latancy: Time from tissue implantation to detection of palpable tumor.

The progress to date is shown below. We have successfully isolated CTCs from several SCLC patients. IHC efforts are underway but have not been successful to date. The injection into mice is not currently being supported by the DOD grant but is shown below to demonstrate feasibility and as a basis for the mouse amendment that will be submitted imminently so these studies can be done as part of the DOD grant and overcome the IHC hurdles (please see CHANGES below).

Opportunities for training and professional development provided by this project

Nothing to report

How were the results disseminated to communities of interest?

- Publication: Faber AC, Farago AF, Costa C, Dastur A, Gomez-Caraballo M, Robbins R, Wagner BL, Rideout WM 3rd, Jakubik CT, Ham J, Edelman EJ, Ebi H, Yeo AT, Hata AN, Song Y, Patel NU, March RJ, Tam AT, Milano RJ, Boisvert JL, Hicks MA, Elmiligy S, Malstrom SE, Rivera MN, Harada H, Windle BE, Ramaswamy S, Benes CH, Jacks T, Engelman JA. Assessment of ABT-263 activity across a cancer cell line collection leads to a potent combination therapy for small-cell lung cancer. Proc Natl Acad Sci U S A. 2015 Mar 17;112(11):E1288-96.

What do you plan to do during the next reporting period to accomplish the goals?

- MGH will perform ongoing CTC collection and analysis from human SCLC patients enrolled on protocol 05-300. The MGH group will also develop CTC-derived xenograft models as described above.

IMPACT

What was the impact on the development of the principal discipline(s) of the project?

Both our study (Faber et al., 2015) and another study (Gardener et al., 2014) assessed the activity of combination Bcl-2 and mTOR inhibition in SCLC and demonstrated strong preclinical activity. Based on these results, clinical investigators on these studies are planning a phase 1/phase 2 study of combination Bcl-2 and mTOR inhibitor therapies. Dr. Hann, Dr. Farago, and Dr. Rudin have submitted a collaborative letter of intent to the Cancer Therapy Evaluation Program (CTEP) at the NCI, and the proposed trial is moving forward in planning stages. This trial will offer a new and innovative therapeutic option for patients with small cell lung cancer.

What is the impact on other disciplines?

Nothing to report.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

Nothing to report.

CHANGES/PROBLEMS

Changes in approach and reasons for change

We have no additional changes to make in our approach beyond what was requested on 9/22/14 and reported in our first annual report.

Actual or anticipated problems or delays and actions or plans to resolve them

The IHC assays on CTCs is not working well. We plan to overcome this problem by using the CTC-derived PDX models to assess the effects of therapeutics on TOR signaling and BCL-2 family bemebers.

Changes that had a significant impact on expenditures

We have no additional changes to make in our budget expenditures other than what was requested on 9/22/14 and reported in our first annual report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards and/or select agents

We have no additional changes to make in use of vertebrate animals, biohazards and/or select reagents beyond what was requested on 9/22/14 and reported in our first annual report. We plan to submit a mouse protocol for the generation of the CTC-derived PDX mice.

PRODUCTS

Publications, conference papers, and presentations

- Published manuscript: Faber AC, Farago AF, Costa C, Dastur A, Gomez-Caraballo M, Robbins R, Wagner BL, Rideout WM 3rd, Jakubik CT, Ham J, Edelman EJ, Ebi H, Yeo AT, Hata AN, Song Y, Patel NU, March RJ, Tam AT, Milano RJ, Boisvert JL, Hicks MA, Elmiligy S, Malstrom SE, Rivera MN, Harada H, Windle BE, Ramaswamy S, Benes CH, Jacks T, Engelman JA. Assessment of ABT-263 activity across a cancer cell line collection leads to a potent combination therapy for small-cell lung cancer. Proc Natl Acad Sci U S A. 2015 Mar 17;112(11):E1288-96

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

- **What individuals have worked on the project?**

Name:	Jeffrey Engelman
Project Role:	PI
Researcher Identifier (e.g. ORCID ID):	No change
Nearest person month worked:	1
Contribution to Project:	No change
Funding Support:	No change

Name:	Erin Sennott
Project Role:	Fellow
Researcher Identifier (e.g. ORCID ID):	No change
Nearest person month worked:	9
Contribution to Project:	Research Fellow
Funding Support:	No change
Name:	Luc Friboulet
Project Role:	Fellow
Researcher Identifier (e.g. ORCID ID):	No change
Nearest person month worked:	6
Contribution to Project:	Research Fellow
Funding Support:	No change
Name:	Hannah Archibald
Project Role:	Technician
Researcher Identifier (e.g. ORCID ID):	No change
Nearest person month worked:	5
Contribution to Project:	Research Technician
Funding Support:	No change
Name:	Eugene Lifshits
Project Role:	Technologist
Researcher Identifier (e.g. ORCID ID):	No change
Nearest person month worked:	6
Contribution to Project:	Research Technologist
Funding Support:	No change
Name:	Max Greenberg
Project Role:	Technician
Researcher Identifier (e.g. ORCID ID):	No change
Nearest person month worked:	4
Contribution to Project:	Research Technician
Funding Support:	No change
Name:	Haichuan Hu
Project Role:	Technician
Researcher Identifier (e.g. ORCID ID):	No change
Nearest person month worked:	3
Contribution to Project:	Research Technician
Funding Support:	No change

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

  Dr. Engelman's Other Support is attached.

- **What other organizations were involved as partners?**
  - Nothing to Report.

SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS

This project is designed as a collaborative project with Dr. Tylers's group at MIT. We have maintained excellent communication with our collaborators about this project and have revised and published a manuscript over the past year. The progress described in this report reflects work done at MGH.

APPENDICES

1. Statement of Work, with proposed modifications included. Please note that this was submitted 9/22/14 to the Department of Defense for review.

2. Other support for Dr. Jeffrey Engelman

APPENDIX 1: *Statement of Work, with modifications included. Please note that this was submitted 9/22/14 to the Department of Defense for review.*

STATEMENT OF WORK – 07/01/2013
PROPOSED START DATE September 1, 2013

Site 1: Massachusetts Institute of Technology Koch Institute for Integrative Cancer Research

500 Main Street

Cambridge MA 02139

Site 2: Massachusetts General Hospital Cancer Center

Building 149

13th Street

Charlestown MA 02129

Initiating PI: Dr. Tyler Jacks

Partnering PI: Dr. Jeffrey Engelman

Specific Aim 1: Determine biomarkers of response and resistance to standard chemotherapy in SCLC GEMMs.	**Timeline**	**Site 1** (Initiating PI)	**Site 2** (Partnering PI)
Major Task 1: Generation of PR and PRP harboring SCLC tumors for use in chemotherapy studies	Months		
Subtask 1: Infection of PR mice (age 6-8 weeks) with adenovirus-Cre. □ Number of mice to infect: 60 **COMPLETED**	1-6	Dr. Jacks	
Subtask 2: Infection of PRP mice (age 6-8 weeks) with adenovirus-Cre. □ Number of mice to infect: 60 **UNDERWAY** MODIFICATION: We will discontinue infection of PRP mice for this project.	1-9	Dr. Jacks	
Major Task 2: Chemotherapy treatment studies in PR and PRP mice harboring SCLC tumors. Modification: Going forward, we propose to limit chemotherapy treatment studies to PR mice.			
Subtask 1: MRI/CT imaging and acute treatment □ PRP mice (months 5-8) **COMPLETED** □ PR mice (months 10-14)	5-14	Dr. Jacks	
COMPLETED			
Subtask 2: Luminescence imaging, MRI/CT imaging, and chronic treatment of mice □ PRP mice (months 5-12) **MODIFIED/DISCONTINUED** □ PR mice (months 10-24) **ONGOING** MODIFICATION: We will continue chronic chemotherapy experiments in PR mice and will discontinue chronic chemotherapy experiments in PRP mice.	5-12	Dr. Jacks	
Major Task 3: Collection and analysis of tissues from chemotherapy treated mice. Modification: These analyses will be conducted primarily in PR mouse tissue.			

Subtask 1: Histologic analysis of acutely and chronically treated mice, including IHC for markers of platinum activity and DNA damage (months 6-18) **UNDERWAY**	6-18	Dr. Jacks	
Subtask 2: Cell line derivation from chronically treated mice (months 9-18) **UNDERWAY**	9-18	Dr. Jacks	
Subtask 3: Protein analysis of tumors from acutely and chronically chemotherapy-treated mice. □ Jacks lab: Collection of frozen tissue and preparation of protein lysate. □ Engelman lab: IHC and Western blotting for Bcl-2, BIM, Mcl-1, Bcl-xL, and PUMA □ Engelman lab: IP for BIM and blotting for associated proteins **UNDERWAY**	9-18	Dr. Jacks	Dr. Engelman
Subtask 4: Identification of differentially expressed transcripts in chemotherapy sensitive vs resistant tumors. □ Preparation of total RNA and submission to biopolymers facility for mRNA sequencing (months 12-18) **UNDERWAY** □ Bioinformatic analysis of data (months 18-24)	12-24	Dr. Jacks	
Major Task 4: Collection and analysis of circulating tumor cells (CTCs) from chemotherapy treated mice.			
Subtask 1: Collect whole blood from mice at time of necropsy **ONGOING**	6-18	Dr. Jacks	
Subtask 2: MODIFIED: CTC collection in the Jacks laboratory using fluorescence activated cell sorting (FACS) to identify TdTomato-expressing tumor cells in whole mouse blood. **UNDERWAY**	6-18	Dr. Jacks	Dr. Engelman

Milestone #1: *Co-author manuscript describing the efficacy of standard chemotherapy in the PR and PRP models, with emphasis on differences between PR and PRP chemosensitivity, apoptotic response to chemotherapy in the acute versus chronic setting, and expression differences between untreated, acutely treated, and chronically treated tumors*	18-24	Dr. Jacks	Dr. Engelman

Specific Aim 2: Perform preclinical study of combination targeted therapy in SCLC GEMMs.			
Major Task 5: Generation of PR and PRP mice for use in combination targeted therapy studies.			
Subtask 1: Infection of PR mice (age 6-8 weeks) with adenovirus-Cre. □ Number of mice to infect: 130 **COMPLETED**	1-9	Dr. Jacks	
Subtask 2: Infection of PRP mice (age 6-8 weeks) with adenovirus-Cre. □ Number of mice to infect: 130 **COMPLETED/DISCONTINUED**	1-12	Dr. Jacks	
Major Task 6: Acute treatment of mice with ABT-263, AZD8055, their combination, or vehicle and subsequent analysis			
Subtask 1: Acute treatments of mice and tissue collection □ MRI/CT imaging and acute treatments of PR and PRP mice □ COMPLETED □ Collection of tumors for histology and protein lysate preparation in PR mice COMPLETED	12-18	Dr. Jacks	
Subtask 2: IHC and western blotting of tumors for P-4EBP1, P-S6, BIM, Bcl-2, Bcl-xL, Mcl-1 from PR tumors **UNDERWAY**	12-30		Dr. Engelman
Subtask 3: CTC capture and analysis □ Jacks lab: Collection of whole blood for CTC capture by (FACS) to identify TdTomato-expressing tumor cells in whole mouse blood. **ONGOING**	12-24	Dr. Jacks	Dr. Engelman

Major Task 7: Chronic treatment of mice with ABT-263, AZD8055, their combination, or vehicle			
Subtask 1: Imaging by luminescence and MRI, and treatment of chemotherapy-naïve mice with targeted therapy in PR mice **COMPLETED**	18-30	Dr. Jacks	
Subtask 2: Treatment of chemotherapy-resistance mice with targeted therapy	21-30	Dr. Jacks	
Milestone #2: *Co-author manuscript describing efficacy of novel combination targeted therapy ABT-263/AZD8055 in genetically distinct models of SCLC (PRP and PR) and in chemotherapy-resistant mSCLC tumors.*	30-32	Dr. Jacks	Dr. Engelman
Specific Aim 3: Utilize patient-derived CTCs as a means to monitor treatment response and predict sensitivity to treatment.			
Major Task 8: Analyze CTCs from SCLC patients at MGH enrolled on DF/HCC protocol 05-300 MODIFICATION: CTCs will be collected using the CTC-iChip technology and directly transplanted into immune compromised mice to generate xenograft models.			
Subtask 1: Enroll patients and collect CTCs. Quarterly enrollment goal: 4 to 5 patients. Overall enrollment goal: 40 patients. **UNDERWAY** **MODIFICATION: overall enrollment goal 20 patients**	6-33		Dr. Engelman
Subtask 2: Analyze CTC number and correlate with radiographic changes in disease CTC quantification is underway We propose to modify this subtask by transplanting isolated CTCs into immune compromised mice to generate xenograft models.	12-36		Dr. Engelman
Subtask 3: Analyze CTCs for P-4EBP1, P-S6, BIM, Bcl-2, Bcl-xL, and Mcl-1 using ISH and IHC We propose performing these analyses on xenografted tumors, in addition to directly in CTCs.	12-33		Dr. Engelman
Milestone #3*: Co-author manuscript describing the utility of human SCLC CTC measurement and analysis for tracking the progression of disease and predicting sensitivity to treatments, with correlation to findings in the mouse models.*	33-36	Dr. Jacks	Dr. Engelman

Projected Quarterly Enrollment for CTC collection under MGH protocol 05-300

	Year 1				**Year 2**				**Year 3**			
Target Enrollment (per quarter)	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**
Site 2: MGH (original)			4	4	4	4	4	5	5	5	5	
MODIFIED target enrollment:			**2**	**2**	**2**	**2**	**2**	**2**	**2**	**3**	**3**	
Target Enrollment (cumulative) (original)			**4**	**8**	**12**	**16**	**20**	**25**	**30**	**35**	**40**	
MODIFIED total enrollment (cumulative)			**2**	**4**	**6**	**8**	**10**	**12**	**14**	**17**	**20**	

Appendix 2: Research Support for Jeffrey Engelman

Active

R01 CA137008 Engelman, Sequist (MPI) 4/1/15-3/31/20 1.2 calendar
NIH-NCI $250,000
Impact of Heterogeneity on Response to EGFR T790M Inhibitors
Competitive renewal of "The Activation of ERBB3 Signaling as a Resistance Mechanism to Targeted Therapies". The goals of this grant are to understand the activity of T790M-specific EGFR inhibitors, also called 3rd-generation EGFR inhibitors.

R01CA140594 Wong, Engelman (MPI) 8/3/09-3/31/18 1.8 calendar
NIH-NCI $143,813 (Engelman)
Therapeutic Strategies for Specific Subsets of KRAS mutant lung cancers
The overall goal of this grant is to develop novel therapeutic strategies that are specifically active against KRAS mutant lung cancers harboring p53 or LKB1 mutations.

Lung Cancer Translational Research Engelman (PI) 8/1/15 – 7/31/18 2.4 calendar
Stand Up to Cancer/American Cancer Society $1,452,559 (MGH)
Targeting KRAS Mutant Lung Cancers
This project develops targeted therapy and immunotherapy approaches to KRAS mutant lung cancers.

1R01 CA164273 Shaw, Engelman (MPI) 2/20/12 – 12/31/16 1.2 calendar
NIH-NCI $207,500
Identification of Resistance Mechanisms to Anaplastic Lymphoma Kinase Inhibitors
This project will explore the molecular mechanisms underlying acquired resistance to crizotinib by generating laboratory models of ALK-positive NSCLC.

P01CA080124 Jain (PI) 5/1/12 – 4/30/17 1.2 calendar
NIH-NCI $24,439
Integrative Pathophysiology of Solid Tumors
Core B: Molecular and Cellular Biology and Morphology
This is a translational program that explores the manipulation of the tumor microenvironment to improve treatment outcome.
Role: Core investigator

P50 CA127003 Fuchs (PI) 7/1/13 – 6/30/18 .6 calendar
NIH-NCI $71,811
DF/HCC SPORE in Gastrointestinal Cancer; Project 3: Defining Novel Therapeutic Strategies for KRAS_Mutant CTC
This project will identify novel targets that synergize with MEK for the treatment of KRAS mutant colorectal cancers.
Role: Project PI

LC120297 Engelman, Sequist (PI) 8/1/13 – 7/31/16 .6 calendar
Dept of Defense-CDMRP $170,000
Deficient BIM Expression and a Mechanism of Intrinsic and Acquired Resistance to Targeted Therapies in EGFR Mutant and ALK-positive Lung Cancers
The goal of this project is to develop a biomarker to predict suboptimal response to therapy and to develop an alternative therapeutic treatment strategy.

Sequist, Engelman, Neal (PI) 10/15/13 – 10/14/16 .12 calendar
LUNGevity $177,357

Determining Mechanisms of Resistance to Next-Generation EGFR Inhibitors
This project will perform repeat biopsies on NSCLC patients with acquired resistance to next-generation EGFR TKIs and assess the tumor material via genotyping, whole genome sequencing and individualized patient-derived laboratory models.

LC120307 Jacks, Engelman (PI) 9/15/13 -- 9/14/16 1.2 calendar
Dept of Defense-CDMRP $137,550

Developing Novel Therapeutic Approaches in Small Cell Lung Carcinoma Using Genetically Engineered Mouse Models and Human Circulating Tumor Cells
This project will apply a genetically engineered mouse model (GEMM) of SCLC to interrogate mechanisms of response and resistance to standard chemotherapy.

R01 CA194535 Jain (PI) 4/1/15 – 3/31/20 .6 calendar
NIH-NCI $228,750

Improving Treatment of Brain Metastases from HER2-positive Breast Cancer
The proposed study aims to demonstrate the NRG-1/HER3 axis as a novel therapeutic target for HER2+ breast cancer brain metastases.
Role: Co-Investigator